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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,435	10/21/2003	Mark F. Pittenger	640100.470	3718

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,435	PITTENGER ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *23-28* is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-21* is/are rejected.

7)☐ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on April 25, 2008, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Joseph T. Woitach/

Supervisory Patent Examiner, Art Unit 1633

Claim Status

Claims 1, 2, 4-10 and 12-28 are pending in the Application, and under current examination. Claims 22-28 were added by the amendment dated June 25, 2007, but were not addressed in the Advisory Action dated July 17, 2007. No claims have been amended, cancelled or newly added.

Response to Claim Objections

Claims 16 and 21 were previously objected to under 37 CFR 1.75(c), for failing to further limit the subject matter of a previous claim. However, upon further consideration, the previous objections are hereby withdrawn.

New Claim Objection

Claim 22 is newly objected to because of the following informalities: The claim recites "cells are administered into an amount effective". An amendment replacing the word "into" with "in" would be remedial. Appropriate correction is required.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1, 2, 4-10 and 12-21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite, and containing language inconsistent with the preamble of the base claims. However, upon further consideration, the rejection of claims 12-21 is hereby withdrawn. The rejection set forth on p. 2 of the Advisory Action dated July 17, 2007 is maintained for claims 1, 2 and 4-10 for reasons of record.

While the intended use of the methods is to produce cardiomyocytes in the heart, or improve ventricular wall motion in the heart, the language contained in the body of the claim makes it unclear whether the cardiomyocytes are actually produced in the heart or elsewhere in the body. As the route of administration is not limited to direct administration into the heart of the individual, the language "wherein said mesenchymal stem cells differentiated into cardiomyocytes", encompasses differentiation into cardiomyocytes at any irrelevant site in the individual.

Applicants argue that the claims clearly encompass multiple routes of administration, and the specification clearly contemplates that mesenchymal stem cells may be administered by a variety of procedures, and a reference ("Lee") cited by the September 22, 2006 Office Action23, states that "[t]ranslplanted stem cells also undergo a 'homing' process in which they are attracted to the site of injury." Thus, those skilled in the art, when reading the claims in light of the specification, would readily understand that, if administered to an individual via a variety of routes of administration (i.e., systemic or localized), the mesenchymal stem cells would travel to the heart, or be delivered to the heart site of injury, in order to produce cardiomyocytes and improve ventricular wall motion. Applicants' arguments have been fully considered, but are not found persuasive.

In response, Applicants should note that a person of skill in the art reading the claims in light of the specification would not be apprised of any homing or traveling of the mesenchymal stem cells to the heart, as such was proposed only in post-filing art. Further, Applicants are referred to the language of base claim 1, in their patent 6,387,369, reciting "producing cardiac muscle cells in the heart of said individual". Similar language is recited in instant claims 12 and 17.

With regard to Applicants' arguments that claims 5-9 limit the route of administration to direct administration, it should be noted that the claims ultimately depend from base claim 4, and thus have been included in the rejection.

Thus, the rejection of claims 1, 2 and 4-10 is maintained for reasons of record.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 12-21 stand rejected under 35 U.S.C.§112, first paragraph, because the specification lacks an enablement for the full scope of the claimed invention. The rejection set forth on pp. 2-3 of the advisory action dated July 17, 2007 is maintained, for reasons of record.

As previously indicated, the specification, while being enabling for a method producing cardiomyocytes and improving ventricular wall motion in a heart of an individual, comprising: administering to the heart of said individual a cardiomyocyte producing amount of autologous or allogeneic mesenchymal stem cells (MSCs), wherein said administered MSCs differentiate into cardiomyocytes in the heart of said individual, resulting in improved ventricular wall motion of the heart, does not reasonably provide an enablement for a method of repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis, by administering autologous or allogeneic MSCs to an individual via any route.

The specification states: "Applicants have discovered that the mesenchymal stem cells may stimulate and/or promote angiogenesis in the heart and/or repair or regenerate blood vessel of the heart" (pp. 9-10, bridging). While the engrafted MSCs were found to express numerous muscle specific proteins, and exhibited morphological changes consistent with myogenesis, the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the

heart. The specification discloses human and rat MSCs transplanted to athymic rats (Examples 1-3), and allogeneic MSCs transplanted by direct injection into infracted pig hearts (Examples 4 and 5, p. 15 and 18; and Fig. 3), resulting in improvements in wall motion scores over time (p. 17) as well as cystolic and diastolic wall thickness (p. 18). The specification discloses that the autologous MSCs were isolated from swine bone marrow, expanded in culture, and cryopreserved until the time of transplantation (p. 18). However, no additional information regarding said culture conditions or any additional alterations to the MSCs are provided. Moreover, while the specification discloses that MSCs were identified surrounding and associated with smooth muscle layer of blood vessels (Example 7, p. 20), it remains unknown whether the MSCs contributed to the formation of said blood vessels, as blood vessels were already present in the infracted pig heart.

The post-filing art of Lee et al. (Ann. Intern. Med. 140: 729-737; 2004; of record) in reviewing the status of stem cell transplantation in myocardial infarction, notes that neovascularization is mediated by endothelial progenitor cells stimulated by GCSF (second column, p. 730). Further noting that autologous bone marrow cells secrete angiogenic factors, such as VEGF and macrophage chemoattractant protein 1, that stimulate the proliferation of endothelial cells (first column, p. 731). The authors conclude that while preliminary data from animal models suggest that infracted myocardium may be regenerated by implanting stem cells, skepticism exists with this treatment method, especially given the initial excitement of angiogenesis studies that did not live up to expectations (second column, p. 735). Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

Applicants traverse the rejection, citing MPEP 2164.02, that an applicant need not have actually reduced the invention to practice prior to filing, and that the previous Office and Advisory Actions provide no evidence, other than mere speculation, that administering mesenchymal stem cells to achieve the effects defined in the claims would not be successful. Further arguing that an *in vivo* animal model example in the specification constitutes a working example, if that example correlates with a claimed method, as mesenchymal stem cells were

administered to a pig, and blood vessels were present in a generalized region of myocardial necrosis, and that mesenchymal stem cells were intimately associated with the smooth muscle layer of the blood vessels, and express proteins that are indicative of angiogenesis. Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is maintained that the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. Localization and association with the smooth muscle layer is not synonymous with repair or regeneration of blood vessels or the promotion of angiogenesis, as the amount or sufficiency of the expressed factors cannot be determined. The association of the MSCs may be with blood vessels already present in the heart tissue. Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues. Further, the allogeneic MSCs in Example 7 were transplanted by direct injection into infracted pig hearts, and not administered by other means. Additionally, the working example does not provide an enablement for formation of blood vessels or angiogenesis, and moreover, a single embodiment does not overcome the art recognized unpredictability for the genus encompassed by the claims.

In response to Applicants' request for evidence, Applicants are referred to a review of mesenchymal stem cells and the treatment of cardiac disease, by Minguell et al. (Exp. Biol. Med. 231:39-49; 2006), wherein the authors describe using a mixture of repair cells that include BM-MNCs, as a source of endothelial progenitors in MI patients for promoting therapeutic angiogenesis. Further describing the ability of MSCs to differentiate into cardiomyocyte-like cells, and to produce angiogenic growth factors, thus providing for co-transplantation of MSCs and MNCs for enhancing angiogenesis (second column, p. 43). Thus, it is clear that MSCs alone appear to be insufficient for generating blood vessels.

In response to Applicants' arguments that no evidence was provided with regards to route of delivery of MSCs, that include intradermal delivery, and that the MSCs would travel to the site of injury, Applicants are referred to a review of cell-based cardiac repair by Ott et al. (Basic

Res. Cardiol. 100:504-517; 2005), wherein the authors state that it stand to reason that local cardiac cell delivery is important, and that it is possible that systemic delivery may simply increase the number of adverse outcomes (second column, p. 508); further stating that with larger cells such as mesenchymal cells, the risk of cellular embolization exists, and that in the chronic heart failure patient, the homing signal to the myocardial scar is very low and engraftment may therefore be too low to be of clinical benefit. In fact, early evidence suggests that after intravenous delivery the majority of the cells are extracted in pulmonary bed, the liver, the lung, spleen and kidney, with only a small portion of the cells localizing to the myocardium. Even more problematic, after intra-arterial delivery in normal canine heart, MSCs resulted in micro-infarcts within the vascular bed downstream of the injection site (second column, p. 509). Thus, the fate of MSCs delivered by routes other than intra-myocardial delivery appear to be unpredictable. As stated in MPEP 2164.05(a), the specification must be enabling as of the filing date. If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993).

The instant claims have been examined in accordance with the *Wands* factors, and in view of the teachings of the post-filing art of record, the high level of unpredictability in transplantation and differentiation of MSCs, and the lack of guidance provided by the specification, it is concluded that the specification does not enable a person of skill in the art to make and use the invention without undue experimentation. Therefore, it is maintained that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis in the heart of an individual, where MSCs are administered by any route to said individual.

Thus, the rejection of claims 12-21 is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 1, 2, 4-10 and 12-21 are not allowed.

Claims 23-28 are considered allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633